Developing Highly Productive Bioprocesses to Prepare for Pandemic Outbreaks

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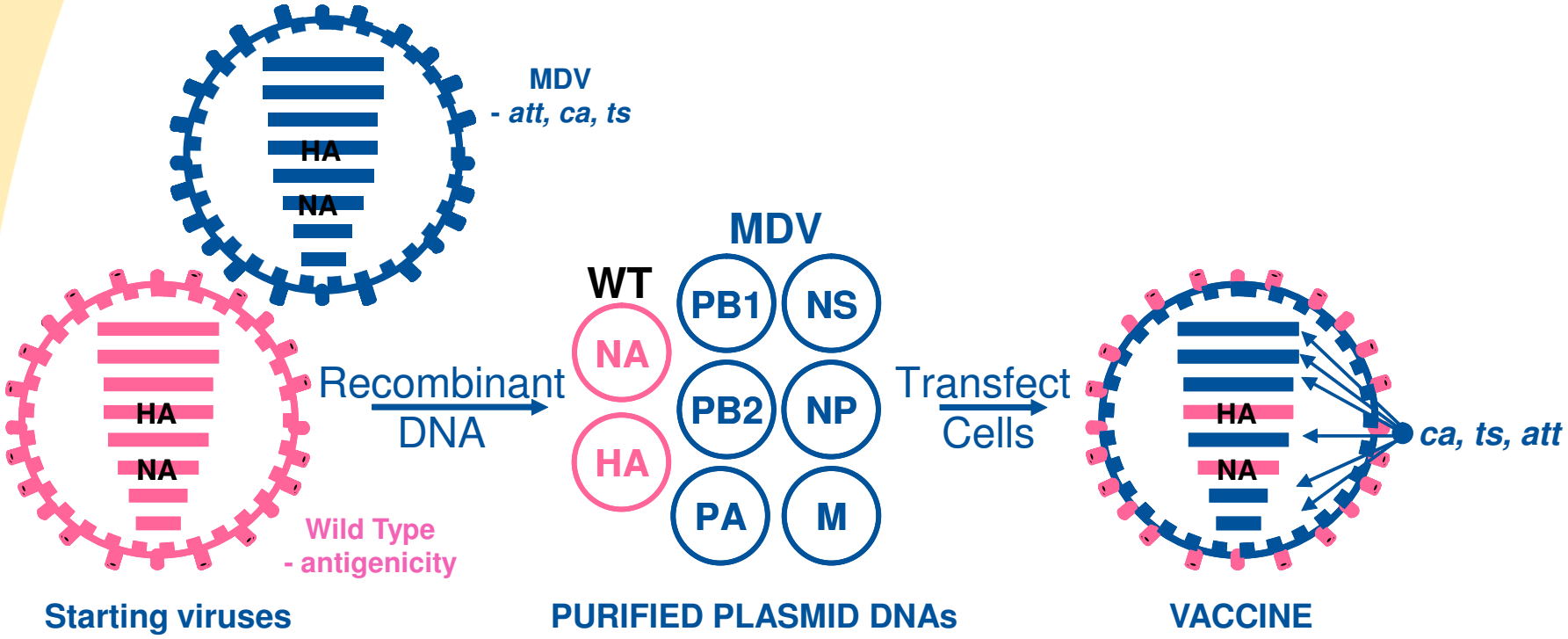
Influenza Vaccines

- Vaccination is the most effective way to prevent infection
  (CDC, 2009 http://www.who.int/mediacentre/factsheets/fs211/en/index.html)

- Two types of vaccines available
  - Inactivated vaccine – i.m.
  - Live attenuated influenza vaccine (LAIV) - Intranasal

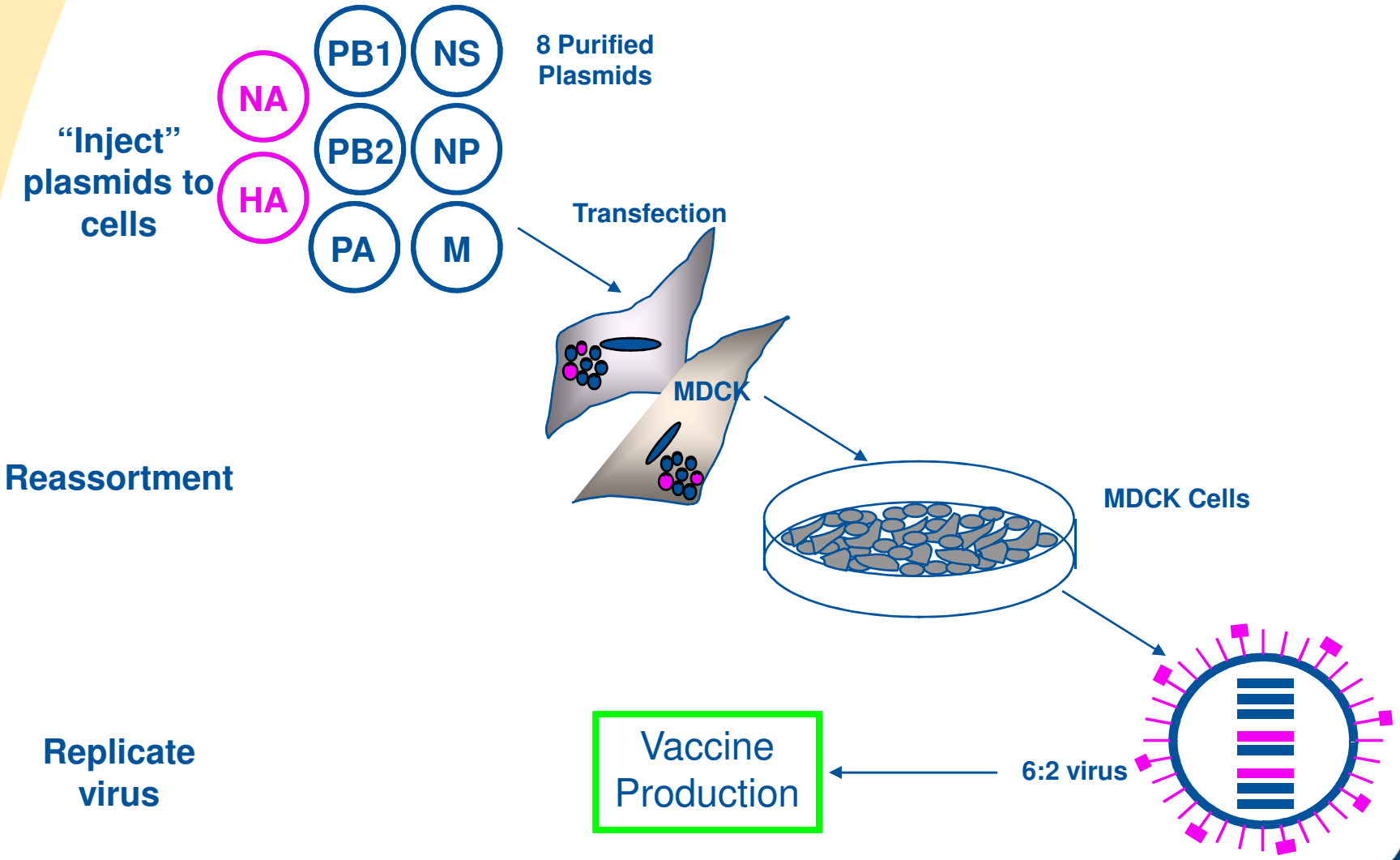
- MedImmune vaccine (LAIV) approved for use in
  - USA
  - Canada
  - Korea
  - HK and
  - other countries

Influenza Vaccines and Reverse Genetics (I)

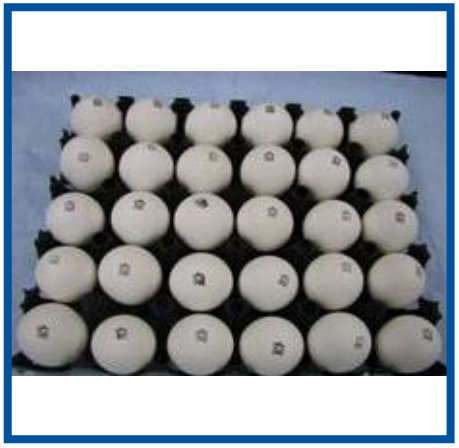


This new technology eliminates the risk from potential wild type virus contaminants

Influenza Vaccines and Reverse Genetics (II)



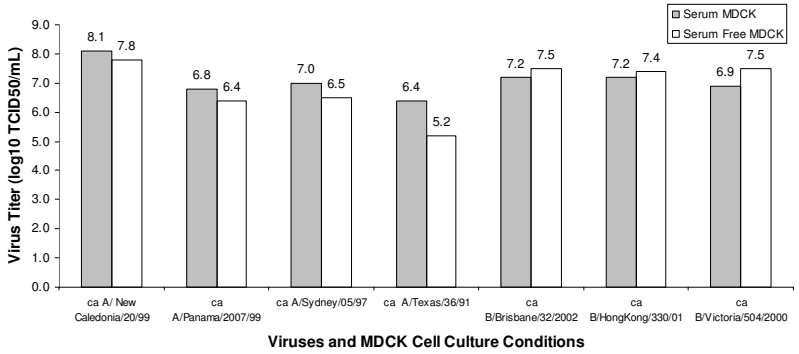
Flu Vaccines and Cell Culture-based Production

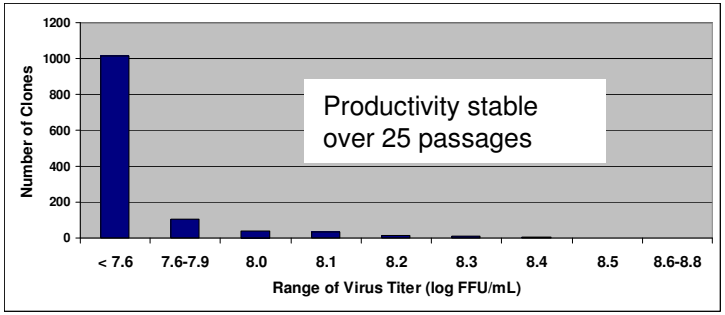


	PRODUCTION SUBSTRATE	
	Eggs (SPF)	Cell Culture
Exposure of flock to environmental agents	Low risk, high impact	NA
Preproduction characterization	- Limited	- Extensive
	- Inherent contamination	- Sterile
Manufacturing procedures	- Need to control contamination	Controlled
Egg allergies limit use	Yes	No
Process scalability	Slow and difficult	Simple

Cell culture-based vaccines provide a robust production platform in pandemic outbreak preparedness

MedImmune MDCK Cells - A Selected Production Cell Substrate





A MDCK cell clone was selected from 13 cell lines based on

- ✓ High productivity
- ✓ Serum free growth
- ✓ Susceptibility to a wide range of flu virus infections
- ✓ Best cell clone out of > 2500 clones (refer to next slide)

MedImmune MDCK Cells - Well Characterized Cell Banks

Test	*Cell Seed*	*MCB*	*WCB*	*ECB*[1]
1. IDENTITY AND PURITY				
Morphology	+	+	+	+
Identification e.g., isoenzymes, immunological and cytogenetic markers, DNA fingerprinting	+	+	+	+
Karyotype	+	+	-	+
Life span (diploid cell lines)	-	-	-	+
Viability	-	+	+	+
Genetic stability (engineered cell lines)	-	+	-	+
2. EXTRANEOUS AGENTS				
Sterility[2]	+	+	+	+/-
Electron microscopy	-	+	-	+
Tests in cell cultures	-	+	+	+
Retroviruses[3]	-	-	-	+
Tests in animals and eggs	-	+	+	+
Selected viruses by molecular methods	-	-	-	+
Antibody-production tests (rodent cell lines[4])	-	-	-	+
Bovine and/or porcine viruses	-	-	-	+
3. BIOLOGICAL CHARACTERISTICS				
Growth Characteristics	-	+	+	+
Tumorigenicity[5]	-	-	-	+
Oncogenicity[6]	-	-	-	+

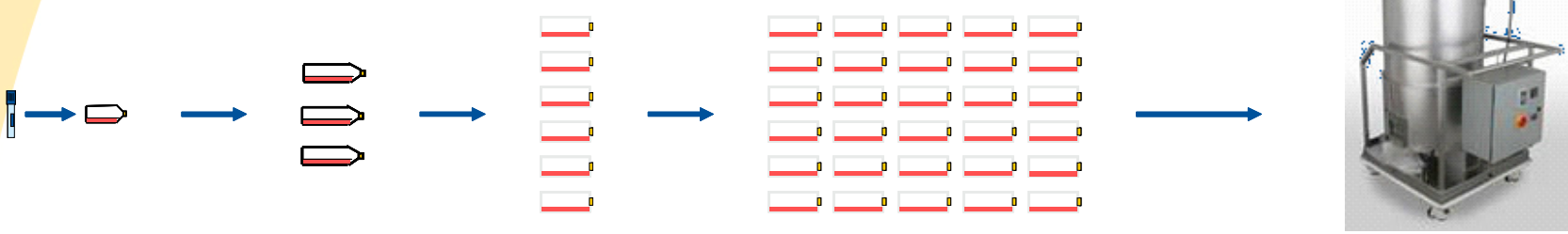
WHO, 4 May 2010

- ✓ **No detectable adventitious agents**
- ✓ **No detectable tumorigenicity and oncogenicity**
- ✓ **Stable beyond End of Production level**

MedImmune MDCK Cells - Similarity of viruses with Commercial LAIV

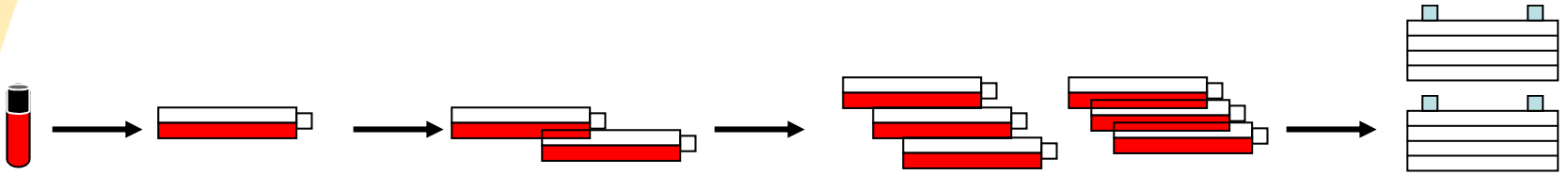
Analytical Test	Comparability between egg and cell produced vaccine
Complete Genomic Sequence	✓
Phenotypic Analysis (*ca* and *ts*)	✓
Host Cell Susceptibility	✓
Virus Protein Expression	✓
Virus Morphology and Size	✓
Replication and Attenuation in Ferrets	✓
Immunogenicity and Efficacy in Ferrets	✓
Safety profile in Animal Models	✓

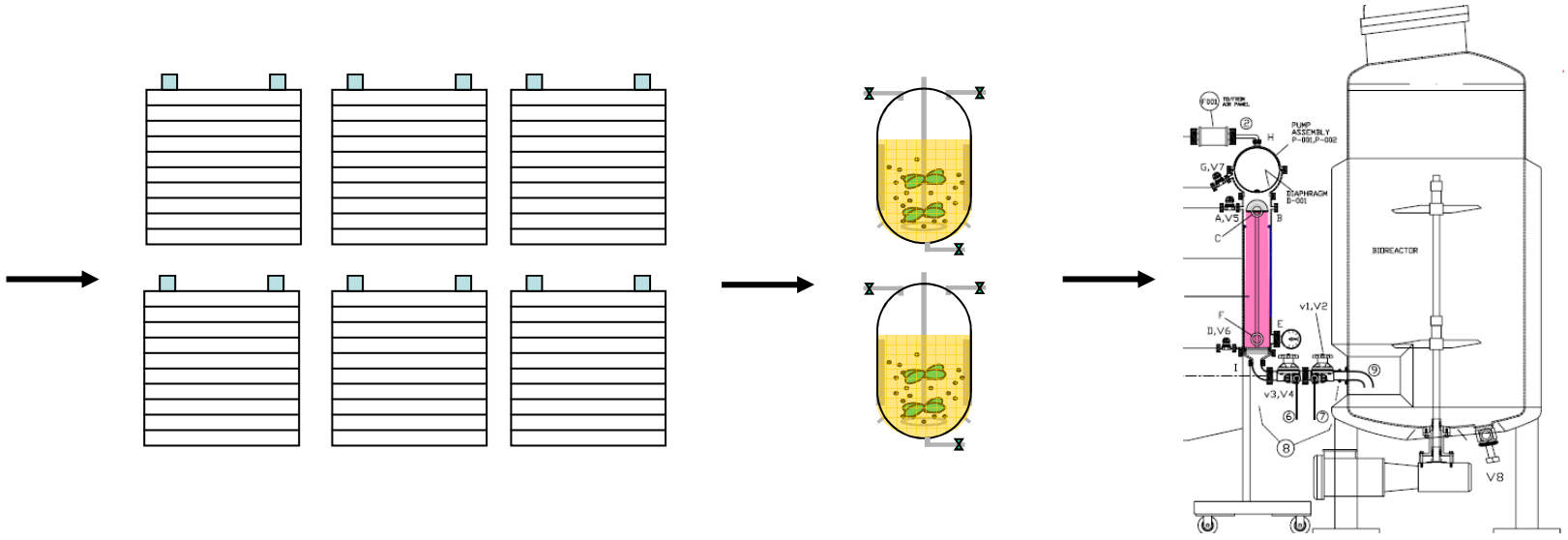
Disposable Culture Vessel-based Manufacturing Process



- **Fully disposable process implemented in GMP Pilot Plant**
  - No need for cleaning/validation with disposable culture vessels
  - Shortened timeline for implementation in clinical production
- **Quick turned-around between batches (in a few hours) making possible to re-start production very rapidly**

Conventional Manufacturing Process - An Alternative Production Platform



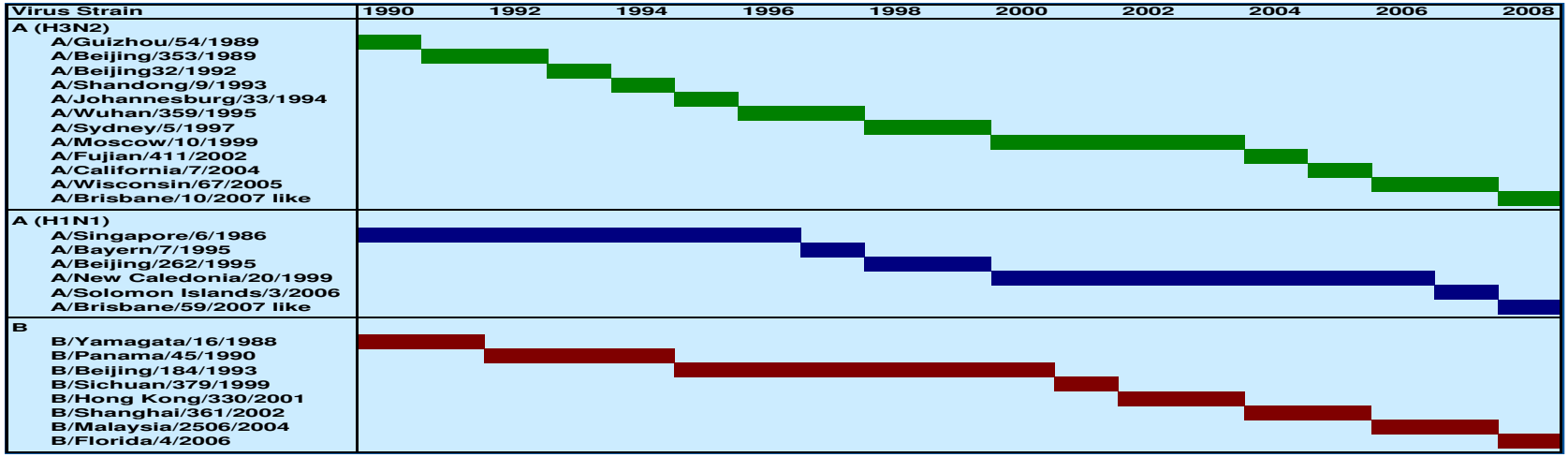


- Also fully developed in MedImmune

Up to 2500 L

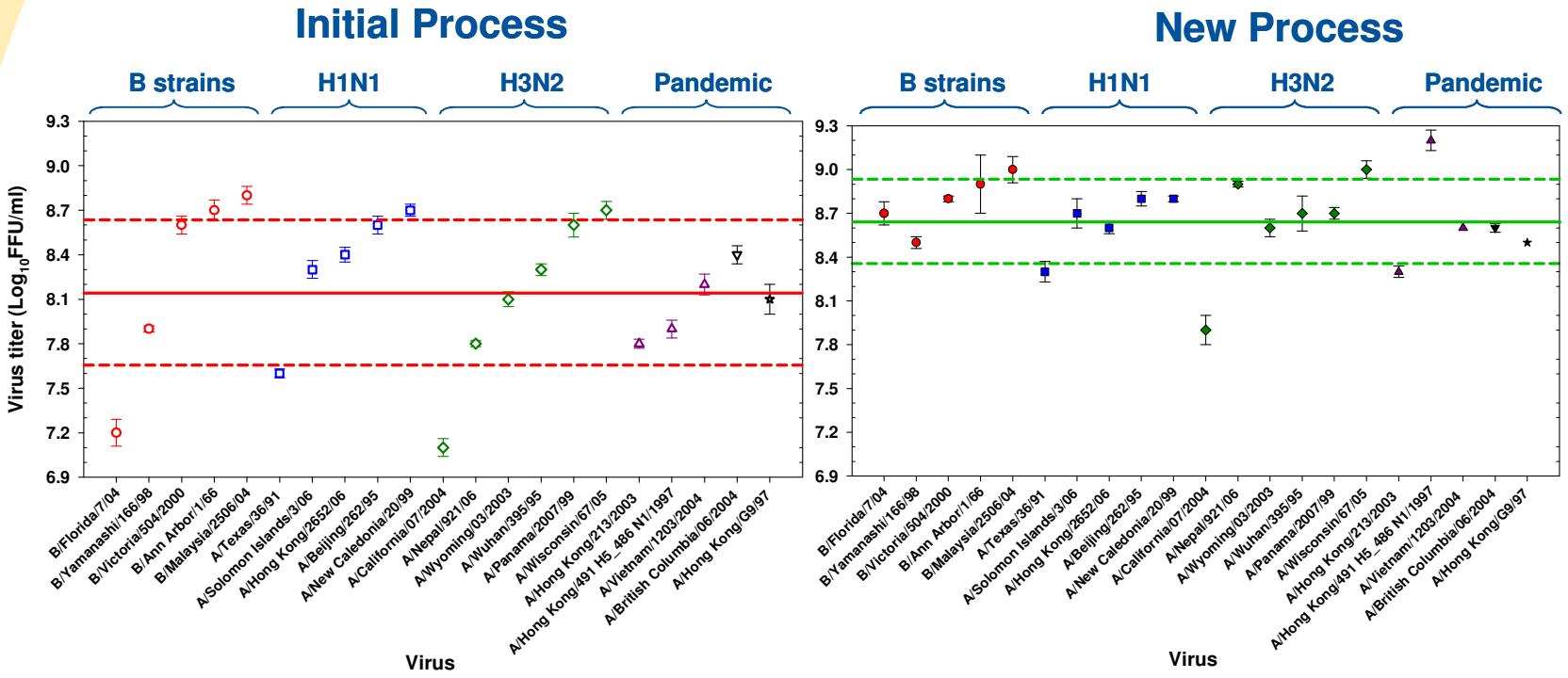
Annual Flu Vaccine Production Timeline

	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
Surveillance												
Selection												
Reassortment												
Manufacturing												
Distribution												
Immunization												



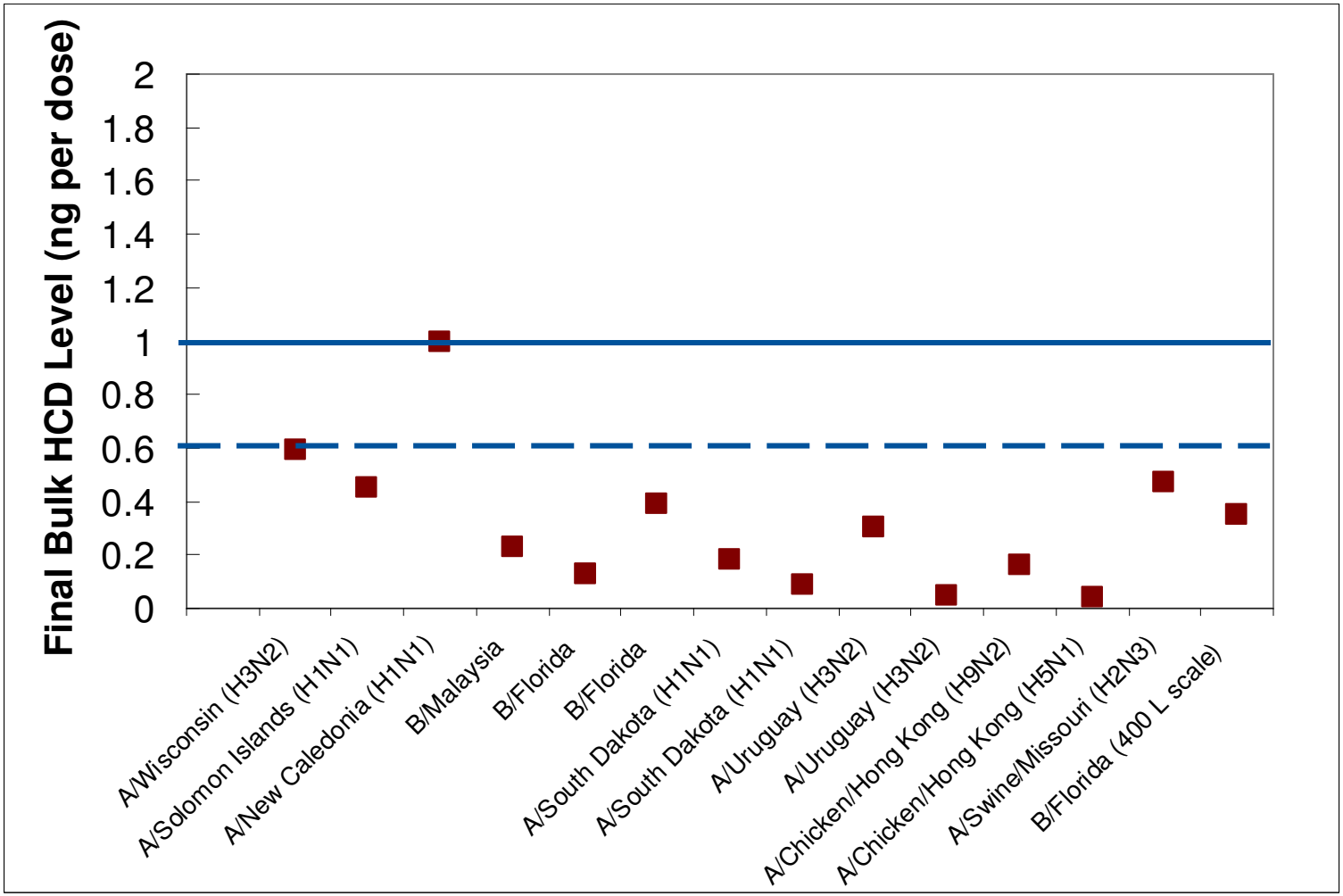
- Frequent vaccine strains and manufacture process changes
- Short (often 1-3 weeks) Process Development Time

Platform Production Reduces Production and Development Time



- Productivity increased 3 - 50 folds through process optimization
- Process robustness improved by identifying process variables and optimizing critical parameters

Low Level of Impurities



Final Bulk DNA Level : ≤ 1 ng per dose

Cell Culture vs. Egg-based Production of Flu Vaccine

Production Time in Weeks*	MDCK Cells**	Eggs***
4	112	26
8	223	52
12	336	78

* million doses of blended vaccine bulk produced
** at 2 x 2000L scale excluding 3 wk lead time (cell thaw and seed train)
*** at 32,500 egg scale excluding lead time (egg procurement)

Large amount of vaccine bulk can be produced in much shorter time using MDCK cells

AstraZeneca

MedImmune

Summary

- **Intranasal administration**
  - simplifies the mass immunization process
- **MDCK cell–based production technology**
  - can produce flu vaccines quickly and in large quantity
- **Disposable technology**
  - minimizes change-over time between runs and leads to significant upfront savings

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Questions

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